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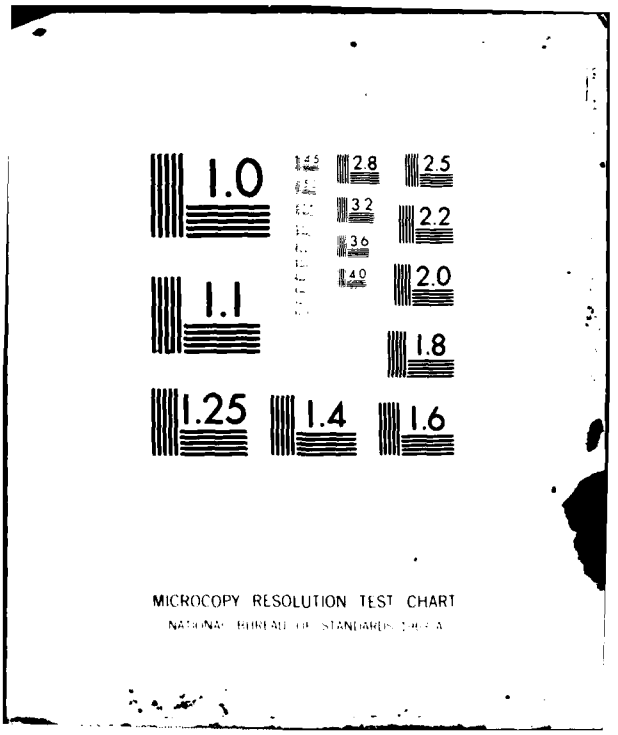
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# MEDICAL MICROBIOLOGY *and* INFECTIOUS DISEASES

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are titrated on an hour-to-hour or minute-to-minute basis, and overtreatment may have serious adverse effects, it is important to monitor the response accurately and quantitatively. Measurement of blood pressure, which is so useful in the initial diagnosis, has only limited usefulness once vasoactive drugs are used, since central arterial pressure may correlate very poorly with tissue blood flow. A more relevant criterion of response is one that measures end-organ performance. The most readily available is urine output, increase in which is usually taken as indicative of increased renal perfusion. Less readily measured on a continuing basis but valuable as an indicator of anaerobic metabolism is serum lactate, which should decrease as the shock state is reversed.

### *PROPHYLAXIS*

Since shock is a complication of severe infection, its prevention lies in the timely and effective treatment of infection when this is possible. One approach is carefully selected antibiotic prophylaxis for invasive procedures likely to be complicated by *local infection or bacteremia, for example*, surgery on the urinary tract (Sullivan et al., 1973), gastrointestinal and biliary tracts (Stone et al., 1976), and pelvic organs (Roberts and Homesley, 1978).

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# METABOLIC EFFECTS OF INFECTION 87

*William R. Beisel, M.D.*

Defensive mechanisms that protect the host against invading microorganisms include the inflammatory, phagocytic, and immunologic responses. In addition, cells throughout the body undergo a variety of predictable changes in their metabolic function during a generalized infection. These metabolic responses account for some of the clinical features of infectious illness.

The predictable metabolic changes during infection can be considered physiologic or homeostatic responses, since they appear to contribute to survival. Because similar metabolic responses occur during infections caused by widely different microorganisms, the responses are said to be generalized or nonspecific. The magnitude and duration of generalized metabolic responses are governed by the severity and persistence of an infectious process rather than by its cause. Thus, generalized infectious illnesses are accompanied by fever, increased oxygen consumption, the need

to generate additional carbohydrate fuels, redistribution within the body of amino acids, lipids, electrolytes, and minerals, increased utilization of vitamins, and hepatic synthesis of enzymes and "acute phase" serum proteins.

Other metabolic changes may be superimposed upon the broad group of physiologic ones. These additional changes are secondary to localization of an infectious process within a major organ. For example, pneumonia can interfere with gas exchange in the lungs, pyelonephritis can cause uremia, and diarrhea can cause a loss of intestinal fluids and electrolytes. Localized infections can thus produce both generalized illness and single organ dysfunction. In some instances, the metabolic consequences of these combinations can become life-threatening in their severity.

## *METABOLIC COSTS OF INFECTION*

Certain daily costs must be met in order to maintain host resistance mechanisms. These costs can be expressed in metabolic terms, since they are based on the need for energy-producing substrates to manufacture cells, precursor components, and molecules important to host resistance. For example, new phagocytes, lymphocytes, and epithelial cells must be produced each day; immunoglobulins and other molecules with unique roles in host defense must also be synthesized. As discussed in the next chapter, malnourished patients become increasingly susceptible to infection if they cannot meet the daily nutritional requirements for maintaining resistance mechanisms.

Because fever causes metabolic rates to increase, additional costs are incurred by the patient with fever. These costs must be met either by using fuels already present in body stores or by increasing the intake of calories and other nutrients.

Because a loss of appetite is common during acute febrile illness, metabolic costs are generally met by mobilizing substrates from tissue stores. This mobilization process can be recognized by measurable losses from the body of nitrogen and the other principal intracellular elements (potassium, phosphorus, magnesium, sulfur, and zinc), and by a loss of body weight and muscle mass. Other metabolic costs are met by changing the patterns of cellular metabolism by using biochemical pathways already available within different tissues. Some of these pathways must be augmented by manufacturing additional enzymes. If an infection is not rapidly controlled, its metabolic costs can deplete body stores of vital nutrients.

Metabolic costs of a curable infection continue to increase until after fever has disappeared, and complete recovery from the metabolic consequences of an infection may require several additional weeks or even months. Depleted nutritional stores make the convalescing patient extremely susceptible to a secondary or superimposed infection by new microorganisms. Until stores can be replenished, it is possible for metabolic losses to initiate a vicious cycle of recurring infections and progressive malnutrition.

## *IMPORTANCE OF HOST METABOLIC RESPONSES DURING INFECTION*

Infectious illness occurs at all ages and is managed by medical practitioners in all specialty fields. Clinicians should understand the biochemical, metabolic, and hormonal events that lead to loss of body nutrients and altered cellular functions. If the clinician can predict the most likely time of onset, magnitude, and duration of important metabolic responses, he should be able to plan optimal supportive care as an adjunct to antimicrobial drug therapy. It is important to anticipate and recognize the special metabolic complications of infection that are immediate threats to survival.

## *INCREASED DEMANDS FOR METABOLIZABLE ENERGY*

One of the principal metabolic effects of a febrile infection is the increase in oxygen consumption. The basal metabolic rate increases about 13 per cent for each degree (Centigrade) rise in body temperature. The increased demand for cellular energy develops at the same time that anorexia causes a decline in food intake.

During simple starvation in the absence of infection, the energy needs of the tissues are met chiefly by lipids. These include free fatty acids obtained from adipose tissue and ketones synthesized from fatty acid precursors within the mitochondria of liver cells. Because the use of glucose is curtailed, less is manufactured. These metabolic adjustments to simple starvation allow the body to conserve protein and amino acid stores and to minimize nitrogen losses.

Infectious illnesses are generally accompanied by a reduction in food intake, but the usual metabolic adjustments to simple starvation are not made. Rather, glucose production is stimulated and ketone body production is inhibited. During infection, readjustments take place in metabolic pathways of individual cells and tissues,

especially in muscle and liver cells. The endogenous metabolism of body fats, carbohydrates, and proteins are all involved in this process. While free fatty acids continue to be used as major sources of fuel, most of the extra requirements for cellular energy are supplied by glucose. Glucose production is speeded up within the liver by using amino acids as major additional substrates. Amino acids move more rapidly than usual from serum into liver cells. At the same time, large quantities of additional glucose-producing free amino acids, namely, alanine and glutamine, are manufactured and released by skeletal muscle for transport via plasma into the liver. Skeletal muscle contains the largest source of "labile" body protein — protein that can be degraded rapidly during an infection to yield free amino acids for use in other tissues. Some of the newly released branched-chain amino acids (leucine, isoleucine, and valine) are oxidized in situ and used for fuel in muscle cells. Nitrogen groups released by this process are used within muscle for the synthesis of alanine and glutamine. The body thus seems willing to degrade the proteins in skeletal muscle and other somatic tissues to produce amino acids that maintain visceral organ functions, generate energy, and manufacture new cells and proteins.

All the sugar-regulating hormones help stimulate or modulate the increased production and release of glucose by the liver. Plasma concentrations of glucagon, insulin, glucocorticoids, catecholamines, and growth hormone increase. Thyroid hormones are also used more rapidly.

The increased hepatic output of glucose leads to high blood glucose values and a larger glucose pool. A speedier turnover of glucose within this larger pool is caused by its increased use as a cellular fuel.

Severe hypoglycemia, accompanied by a fall of body temperature to subnormal values, can occur if the liver fails to maintain its output of glucose. Failure of hepatic glucose production is generally due to one of two basic mechanisms: (1) depletion of the supply of substrates or (2) failure of the molecular mechanisms required for producing glucose (hepatic cell failure).

Substrate depletion accounts for severe hypoglycemia during bacterial sepsis in newborns. Because infants are born with little skeletal muscle, their stores of "labile" protein are too limited to support a prolonged need for glucose production.

Failure of hepatic cells is usually caused by direct injury to the cells by viruses, such as hepatitis or yellow fever viruses, or by bacterial products such as endotoxin. Liver cells may also fail to synthesize glucose during the terminal stages of overwhelming infections.

## *ALTERATIONS IN LIPID METABOLISM*

In addition to producing more glucose during acute infections, liver cells accelerate lipid metabolism. The hepatocellular uptake of plasma free fatty acids is increased. Production of triglycerides within liver cells is accelerated and more triglycerides move into the plasma. Some triglycerides may also accumulate as droplets in liver cells and cause fatty metamorphosis.

On the other hand, less free fatty acids are used for the synthesis of ketone bodies than would normally be expected during fasting. Increased release of insulin from the pancreas, a common secondary manifestation of generalized infection, and the lipogenic action of insulin on hepatic cells account for this curtailment in production of ketone bodies. As a result, ketone bodies are not made available to meet body energy requirements. Curtailment of ketone body production is thus a physiologic hormonal response during infection rather than a pathologic breakdown of biochemical pathways.

According to evidence obtained with isotope tracers, the liver, in addition to increasing its output of triglycerides, produces and releases more cholesterol and phospholipids during infection. Since these lipids are all released into plasma as lipoproteins, the liver must produce lipid transport proteins, but little is known about the mechanisms that regulate the rates of lipid release into plasma. However, changes in plasma lipid concentrations are controlled by the rates of lipid removal (or utilization) as well as by changes in the rates of lipid production. Plasma cholesterol, phospholipid, free fatty acid, and triglyceride values vary individually during different infections or even during different stages of a single infection. A massive accumulation of triglycerides is consistently observed during gram-negative sepsis and may give the plasma a milky appearance. Triglycerides accumulate because of increased hepatic production and decreased activity of the lipolytic enzymes that initiate cellular removal of triglycerides from plasma.

## *CHANGES IN PROTEIN AND AMINO ACID METABOLISM*

All aspects of protein metabolism are affected by infection. Every host defense mechanism depends on the presence or function of some kind of body protein, whether it is a cellular enzyme, a structural protein, a cell membrane receptor, an immunoglobulin, a transport protein, a compo-

nent of the complement, kinin, or coagulation systems, or some other plasma protein. Infection causes cells to speed up the production of some proteins, to slow the production of others and at the same time to break down "labile" body proteins into free amino acids.

During acute infections, plasma albumin values decline. The catabolism of skeletal muscle proteins exceeds their rate of production, and increased quantities of free amino acids are released into plasma. Despite the entry of more free amino acids into plasma, there is a still greater increase in uptake of amino acid by the liver. As a result, plasma concentrations of most free amino acids decline, especially the branched-chain group.

Free amino acids are used to produce phagocytic and lymphoid cells and to maintain the functional and structural integrity of other tissues. The liver also increases production of certain enzymes and the "acute phase" plasma proteins. These include C-reactive protein, haptoglobin, alpha$_1$-antitrypsin, ceruloplasmin, fibrinogen, and others.

Before amino acids are used for producing glucose, their amino nitrogen must be removed from the carbon skeleton. This nitrogen is converted into urea within the hepatic cells and excreted in the urine. Increased free tryptophan in liver cells is shunted into the serotonin pathway or degraded via the kynurenine pathway for excretion as urinary diazo-positive reactants.

Because of the increased use of amino acids to produce glucose and urea, losses of nitrogen in the urine are high during the acute stages of most febrile infections. Additional nitrogen is lost by sweating, by vomiting or diarrhea, or by nasal secretion and sputum production during respiratory tract infections. The diminished intake of nitrogen-containing foods in combination with continued losses causes negative nitrogen balance.

Nitrogen balance does not become negative during the incubation period of an infection, but begins to be negative soon after the onset of fever. Losses of body nitrogen may reach 10 to 15 g per day if fever is high; cumulative total losses may exceed 100 g during the course of an acute illness. Large daily losses of nitrogen cannot be sustained indefinitely. If an infection becomes subacute or chronic, the body again approaches a state of nitrogen equilibrium, but at a cachectic level.

After recovery, nitrogen balance should become strongly positive as degraded proteins are resynthesized. The process of rebuilding nitrogen stores can be speeded up by increasing the dietary intake of high quality protein foods, especially during early convalescence.

## *CHANGES IN MINERAL METABOLISM*

Principal body minerals undergo a complex variety of changes during acute infection. Large amounts of some minerals are lost from the body, while others show either a physiologic redistribution or a sequestration in certain tissues. Minerals of soft tissue are lost during acute infections roughly in parallel with the losses of body nitrogen. The negative balances are caused by the combination of diminished dietary intake plus losses in the urine or feces of magnesium, phosphorus, potassium, sulfur, and zinc. Change in calcium stores is generally minimal unless long-term immobilization is a component of the illness, as in paralytic poliomyelitis. Similarly, deficits of body phosphorus appear to reflect losses from soft tissue rather than bone.

Although negative phosphorus balance generally parallels that of nitrogen, phosphorus losses during the period of early symptoms are also influenced by changes in acid-base balance. When fever occurs, respiratory rates become faster. The increased loss of carbon dioxide causes respiratory alkalosis accompanied by a transient disappearance of phosphorus through sweat and urine. During infections characterized by severe or protracted diarrhea, potassium ions escape by way of the intestine. This loss of potassium from the tissues may be large enough to produce the vacuolar changes in kidney tubules and myocardial cells characteristic of potassium deficiency.

Each of the three most widely studied essential trace minerals—iron, zinc, and copper—undergoes an abrupt redistribution within the body during infectious illnesses. These changes are under physiologic control mechanisms and are stimulated by inflammatory responses and activation of phagocytic cells. The concentrations of iron and zinc abruptly decline in the plasma as they are taken up by the liver. These two minerals become physiologically "sequestered" within cellular storage sites. Iron is held as hemosiderin or ferritin, while zinc is bound within liver cells to newly synthesized metallothionein. Copper, on the other hand, is secreted by the liver into plasma as a component of newly synthesized ceruloplasmin.

A rapid decline in plasma iron and zinc concentrations may precede the onset of fever, while the increase in plasma copper follows soon afterward. Since only the "loosely bound" fractions of plasma zinc move into the liver, plasma values of zinc rarely fall more than 50 per cent. In contrast, plasma iron may fall to undetectable values, leaving the iron-binding capacity of plasma almost entirely unsaturated. At the same time,

plasma copper and ceruloplasmin values may double or triple.

Physiologic sequestration inhibits the incorporation of iron into hemoglobin and eventually causes the "anemia of infection." This process cannot be reversed by oral or parenteral iron. In addition to its temporary sequestration within the liver, appreciable quantities of zinc may be lost in the urine. The redistribution of iron, zinc, and copper are reversed after recovery from infection. Little is known about the responses of other trace minerals.

## *CHANGES IN ELECTROLYTE AND WATER METABOLISM*

Fluid and electrolyte responses vary greatly during different infectious diseases. Imbalances can cause death, either from severe dehydration or from fluid overload.

In most acute infections, an increased adrenal output of aldosterone during fever causes renal tubular cells to reabsorb sodium and chloride. This mechanism accounts for the virtual disappearance of these electrolytes from urine and their retention in body fluids, and for a secondary increase in the extracellular fluid volume. Recovery from an acute period of fever may be followed by diuresis in early convalescence.

Retention of body water can also be caused by "inappropriate" secretion of antidiuretic hormone from the posterior pituitary. This phenomenon is common in infections of the central nervous system and may occur during severe generalized infections. Some severe infections may also be complicated by the accumulation and sequestration of sodium within cells that results in declining plasma sodium concentrations. Attempts to correct low sodium values with saline may lead to acute cardiac failure or cerebral edema. If low plasma sodium values during severe infections cannot be explained by losses from the body, the patient should be managed by careful restriction of fluid and sodium intake until the total daily urine volume consistently increases.

On the other hand, diarrhea may produce massive loss of extracellular fluids and electrolytes. In cholera or severe enterotoxic diarrhea, fluid loss may lead to hypovolemic shock and death. Therapy requires prompt resuscitation with isoosmotic saline and correction of concomitant acidosis and potassium deficiency.

## *ACID-BASE DISTURBANCES*

Pathogenic mechanisms may produce a wide variety of acid-base abnormalities during different kinds of infections. Rapid breathing during fever causes excessive loss of dissolved carbon dioxide from the blood and a transient period of uncompensated respiratory alkalosis. In contrast, pneumonia that prevents ventilatory exchange of pulmonary gases leads to oxygen deficits and carbon dioxide retention with respiratory acidosis. Respiratory acidosis can also result from acute poliomyelitis or tetanus, both of which can cause neuromuscular abnormalities that prevent the thoracic movements required for breathing.

Increased cellular generation of organic acids may produce metabolic acidosis. Septic shock or localized capillary-bed stasis can lead to cellular hypoxia, which increases lactic acid production and the severity of metabolic acidosis. Acute intestinal loss of bicarbonate during severe diarrhea can also produce acute metabolic acidosis. On the other hand, the cumulative loss of body potassium that accompanies protracted diarrhea can lead to secondary chronic metabolic alkalosis.

## *ENDOCRINE RESPONSES*

As alluded to above, certain hormonal actions help to modulate salt and water metabolism and energy-generating responses during infection. In contrast, several major hormones, including thyroid and parathyroid hormones, certain pituitary trophic hormones, and the gonadal steroids have no clearly defined role.

The adrenal glucocorticoid hormones serve a central but largely "permissive" role. These steroids are necessary to allow some molecular mechanisms to function in hepatic cells. The adrenal secretion of cortisol increases several fold early in the course of fever. This increase in cortisol secretion is accompanied by smaller increases in the adrenal output of ketosteroids and pregnanetriol. These increases do not persist beyond the onset of recovery. Increased adrenal output is never of sufficient magnitude or duration to produce negative nitrogen balances or the other physiologic changes known to accompany the administration of pharmacologic doses of synthetic glucocorticoid hormones.

Failure of hepatic enzyme systems during overwhelming infections may permit the plasma concentration of cortisol to reach unusally high levels. Conversely, destruction of the adrenals by infection prevents steroid production and leads to death unless this complication is recognized and treated. If an infection becomes subacute or chronic, steroid output also falls into a subnormal range.

Substances released by phagocytes and lymphocytes also have hormone-like functions that

can stimulate both local and generalized physiologic responses. These biologically active products include prostaglandins, lymphokines, enzymes, and endogenous mediators such as those that initiate fever, mobilize neutrophils, or cause trace mineral redistribution.

## *SUMMARY*

Generalized infectious illnesses are accompanied by a broad group of metabolic, biochemical, and endocrinal responses. Although caused by many different molecular mechanisms, generalized metabolic changes occur in relatively predictable patterns related to the onset, severity, and duration of fever. These changes include the catabolism of skeletal muscle proteins, acceleration of hepatic gluconeogenesis, ureagenesis and lipogenesis, inhibition of ketogenesis, retention of extracellular salt and water, loss of major intracellular elements, and redistribution within the body of certain trace minerals. Other metabolic changes develop if an infection becomes localized in a predominant organ system. Some metabolic consequences of infection, which include hypoglycemia, hypovolemia, fluid overload, and failure of various key organs, are life-threatening.

The views of the author do not purport to reflect the positions of the Department of the Army or the Department of Defense. (Para. 4-3, AR 360-5.)

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# 88 MALNUTRITION AND INFECTION

Gerald T. Keusch, M.D.

*Sorrow may be fated, but to survive and grow is an achievement all its own.*

R. COLES
*Children of Crisis, 1964*

Malnutrition of the affluent as well as the poor, whether because of excess, insufficiency, or inappropriate choice of foods, is a common malady throughout the world. In developing countries the most common clinical forms of malnutrition are due either to insufficiency of food per se, resulting in marasmus, or to inadequacy of specific nutrients in the diet including protein, vitamin A, or iron, resulting in kwashiorkor, xerophthalmia, and anemia, respectively. However, such "pure" inadequacies rarely exist, and it is reasonable to suggest that most malnutrition is caused by a lack of both protein and calories, for which the term protein-calorie malnutrition (PCM) will be used. Upon this base of PCM are engrafted specific nutrient inadequacies that differ in type from one country to the next.

In developing nations the youngest in society are the principal targets of PCM. In industrialized nations adults are at greatest risk, developing PCM secondary to debilitating chronic diseases, neoplasms, alcoholism, inflammatory bowel disease, or renal failure. Recently, adult PCM has also been recognized in hospitalized patients who are maintained on the routine, semistarvation regimens of parenteral fluid and electrolytes during the treatment of many acute medical and surgical illnesses. In both situations malnutrition greatly exaggerates both the susceptibility to infectious agents and the severity of the illnesses they produce. Because infection itself causes losses of nutrients by a number of mechanisms, the interaction of infection and malnutrition may lead to progressive debilitation and increased mortality. This interaction has been termed "synergistic," but it is difficult to define this synergism precisely. The minimum consequence in young children is impaired growth that may result in permanent stunting and failure to achieve optimal intellectual potential. In adult PCM, the analogous end of the spectrum may be impaired wound healing or infection that pro-